Remarks

Claims 41, 42 and 46 of this application were rejected in the Office Action mailed on March 7, 2006. Applicants have amended claims 41, 42 and 46 to provide the method of inhibiting HIV replication. The amendment of these claims does not add any new matter, and is supported by the original specification. For example, page 25, lines 24 through 31, provide that the compounds according to the invention "...may be used in the treatment and prevention of any of the diseases or conditions mediated by or associated with CCR5 chemokine receptor modulation, particularly infection by human immunodeficiency virus, HIV. The use of such combinations of therapeutic agents is especially pertinent with respect to the treatment and prevention of infection and multiplication of the human immunodeficiency virus, HIV, and related pathogenic retroviruses within a patient in need of treatment or one at risk of becoming such a patient."

Accordingly, claims 41 to 42, and 46 are currently pending in the instant application.

Claim Rejections Under 35 USC § 112, 2nd ¶

Claims 41, 42 and 46 were rejected "under 35 USC 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is mostly nearly connected, to make and/or use the invention." Applicants respectfully disagree, and respond to the Examiner's assertions concerning the relevant Wands factors in turn.

The Nature of the Invention

The Examiner noted that the nature of the invention is the method of treating HIV infection in a mammal. Upon entry of the foregoing amendment, the claims recite a method of inhibiting HIV replication in a mammal. Applicants believe the invention is fully enabled by the specification for making, formulating, administering, and testing compounds according to the invention.

First, the specification provides enabling support for making compounds of the present invention. For example, see page 5, line 5, through page 19, line 30. This description for making compounds according to the invention provides, *inter alia*, 6 schemes that would be readily understood by one of ordinary skill in the art. Accordingly, Applicants respectfully submit that the making of compounds according to the invention is fully enabled by the specification as originally filed.

Second, the specification provides enabling support for formulating the compounds of the invention. For example, see page 21, line 23, through page 22, line 28. Please note that page 22, lines 5 to 15 contains a specific example of a formulation for a 10 mg tablet. Accordingly, Applicants respectfully submit that the formulations incorporating compounds according to the invention are fully enabled by the specification as originally filed.

Third, the specification provides enabling support for administering the compounds of the invention to inhibit HIV replication. For example, see page 21, lines 10 through 22, and also see page 22, line 29, through page 25, line 4. Note that the compounds may be administered in various forms, through various routes, and in combination with additional therapeutic agents and active ingredients (see page 25, line 20, through page 27, line 28 of the specification). Accordingly, Applicants respectfully submit that the administration of compounds according to the invention is fully enabled by the specification as originally filed.

Fourth, the specification provides enabling support for testing of the compounds according to the invention. For example, see page 62, lines 5 through 8. This biological activity data also demonstrates effective use of the compounds according to the invention for targeting the CCR5 receptor Accordingly, Applicants respectfully submit that the testing of compounds according to the invention is fully enabled by the specification as originally filed.

Moreover, the method of inhibiting HIV replication in a mammal is supported by the specification in multiple locations, as described above. For example, please see: (1) page 20, lines 3–8; (2) page 20, lines 26–31; (3) page 25, line 23, to page 26, line 24; and

(4) page 27, line 1, to page 29, line 5. These disclosures in the specification clearly enable the method of inhibiting HIV replication in a mammal.

Applicants respectfully assert that the making, formulating, administering, and testing of compounds according to the invention, as well as the method of inhibiting HIV replication in a mammal, are all clearly enabled by, and sufficiently described in, the specification as originally filed.

The State of the Prior Art and Predictability

The Examiner asserted that "[t]here is no nexus between CCR5 and curing/preventing HIV. Chemokine CCR5 receptors are known to be associated with inflammatory diseases. At the time of the invention there was no umbrella drug known to cure/prevent HIV." Applicants respectfully disagree with the Examiner's assertions.

As provided by the Federal Circuit, the test of enablement is "whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." United States v. Telectronics, Inc., 857 F. 2d 778, 785 (Fed. Cir. 1988).

Here, Applicants have provided ample enabling support in the specification for the claimed methodology (see discussion under **The Nature of the Invention**, above). Also, the state of the prior art at the time of the application filing date (June 2000 for the provisional application) clearly supports a nexus between CCR5 and curing/preventing HIV. The following representative references pre-dating the current application are instructive. Copies of these references are provided in the accompanying IDS filed together with this Response.

June 1996

Choe et al., **The β–Chemokine Receptors CCR3 and CCR5 Facilitate Infection by Primary HIV–1 Isolates**, *Cell*, Vol. 85, , June 28, 1996, pp. 1135-1148.

This reference provides that "in addition to CD4, members of the chemokine receptor family play critical roles in early events in HIV-1 infection... [T]he clinically relevant, macrophage-tropic HIV-1 can use other members of the chemokine receptor

family, such as CCR3 and CCR5, to facilitate infection." Further, Choe notes that "the enhancement of primary virus infection by CCR3 and CCR5 appears to be specific and is not merely a result of higher surface expression of these receptors." Further, the reference provides that "in addition to CD4, members of the chemokine receptor family play critical roles in early events in HIV-1 infection. ... [and] the clinically relevant, macrophage-tropic HIV-1 can use other members of the chemokine receptor family, such as CCR3 and CCR5, to facilitate infection."

May 1998

Littman, **Chemokine Receptors: Keys to AIDS Pathogenesis?**, Cell, Vol. 93, May 28, 1998, pp. 677-680.

This reference provides that "CCR5 ... is the major cofactor required for entry of macrophage-tropic strains of HIV-1 into $CD4^+$ cells." Further, the reference also notes that "[t]he chemokine receptor is the primary receptor that both binds envelope glycoprotein and triggers fusion." Moreover, Littman notes: "The finding that chemokines can inhibit HIV replication by blocking viral entry has provided the impetus to develop compounds that will interfere with HIV binding to CCR5 and CXCR4. Because the absence of CCR5 does not appear to result in a significant phenotype, blocking of CCR5 function with specific agents is likely to be well tolerated."

June 1998

Zhang et al., **In Vivo Distribution of the Human Immunodeficiency Virus/Simian Immunodeficiency Virus Coreceptors: CXCR4, CCR3, and CCR5**, *Journal of Virology*, Vol. 72, No. 6, June 1998, pp. 5035–5045.

This reference provides that "eight coreceptors ... have been found to play an essential role in HIV/SIV entry. ... Among these coreceptors, CXCR4, CCR3, and CCR5 are the major ones used by HIV isolates for efficient entry."

November 1998

Zhang et al., **Chemokine Coreceptor Usage by Diverse Primary Isolates of Human Immunodeficiency Virus Type I**, *Journal of Virology*, Vol. 72, No. 11, November 1998, pp. 9307–9312.

This reference provides that "despite the number of chemokine receptors implicated in viral entry, CCR5 and CXCR4 are likely to be the physiologically relevant chemokine receptors used as entry cofactors in vivo. ... Thus, these results and the results of others strongly suggest that CCR5 and CXCR4 are the physiologically most relevant chemokine receptors used for virus entry by diverse strains of primary viruses isolated from peripheral blood."

Based on information from these representative references, Applicants respectfully submit that one of skill in the art would clearly understand the patent specification as providing clear direction in using the compounds of the present invention to inhibit HIV replication in mammals without any undue experimentation. Further, the state of the art at the time of filing based on the above articles provides evidence that an inhibitor targeting CCR5 would be desirable for inhibiting HIV replication in mammals. While Applicants agree with the Examiner's statement that CCR5 receptors are also known to be associated with inflammatory diseases, the reference articles also provide clear indication that the CCR5 receptor was also known to be associated with HIV cell entry.

Guidance and Working Examples

The Examiner asserted that "[t]he claims are drawn to preventing or curing HIV infection. The claims are not enabled for this breadth of scope. Applicants have not shown the claimed compounds effective preventing or curing H[I]V." The Examiner further asserted that "CCR5 binding is known to be associated with inflammatory diseases. There is no nexus between CCR5 and treating HIV." Applicants respectfully disagree with the Examiner's assertions.

As discussed above, the prior art at the time of filing clearly established a nexus between the CCR5 receptor and HIV cell entry. Further, as noted in the March 2, 2000

Progenics press release provided herein: "These new findings pinpoint the CCR5 structures that HIV recognizes during infection of target cells. The discovery is important both for our understanding of AIDS pathogenesis and for the design and development of CCR5-targeted fusion inhibitors." Thus, the prior art evidences that a clear nexus existed between CCR5 and treating HIV at the time the instant application was filed.

The Examiner also provided notice as to the biological data contained in the specification as originally filed. This data clearly shows that the tested compounds of the invention all yielded an IC_{50} value of less than 10 nM, which data indicates the relatively high potency of the compounds in targeting CCR5 to inhibit HIV replication.

Applicants also provide herein further compelling data as to the potency of the compound in Examples 4, 6 and 7 (also known as UK-427857). See Fatkenheuer et al., **Efficacy of Short-term Monotherapy With Maraviroc, a New CCR5 Antagonist, in Patients With HIV-1**, *Nature Medicine*, Volume 11, Number 11, November 2005, pp. 1170–1172. This reference provides clear proof of concept that CCR5 antagonism is a viable antiretroviral therapeutic approach, as described and enabled in the specification, and later confirmed in human clinical trials.

Accordingly, Applicants respectfully assert that all the rejections have been overcome and should be withdrawn. Applicants respectfully request withdrawal of the rejection under 35 USC § 112, 2nd Paragraph.

Early notice of allowance of this case is requested.

Conclusion

Applicants respectfully request that a timely Notice of Allowance be issued in this case.

If any fee is required for the filing of this response, including extensions of time for which Applicants hereby petition, please charge all such required fees to Deposit Account No. 500329.

Respectfully submitted,

/Keith D. Hutchinson/

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